The role of the fetal biophysical profile in the management of fetal growth restriction

Ahmet A. Baschat, MD; Henry L. Galan, MD; Wesley Lee, MD; Greggory R. DeVore, MD; Giancarlo Mari, MD; John Hobbins, MD; Anthony Vintzileos, MD; Lawrence D. Platt, MD; Frank A. Manning, MD

Growth-restricted fetuses are at risk of hypoxemia, acidemia, and stillbirth because of progressive placental dysfunction. Current fetal well-being, neonatal risks following delivery, and the anticipated rate of fetal deterioration are the major management considerations in fetal growth restriction. Surveillance has to quantify the fetal risks accurately to determine the delivery threshold and identify the testing frequency most likely to capture future deterioration and prevent stillbirth. From the second trimester onward, the biophysical profile score correlates over 90% with the current fetal pH, and a normal score predicts a pH >7.25 with a 100% positive predictive value; an abnormal score on the other hand predicts current fetal acidemia with similar certainty. Between 30% and 70% of growth-restricted fetuses with a nonreactive heart rate require biophysical profile scoring to verify fetal well-being, and an abnormal score in 8% to 27% identifies the need for delivery, which is not suspected by Doppler findings. Future fetal well-being is not predicted by the biophysical profile score, which emphasizes the importance of umbilical artery Doppler and amniotic fluid volume to determine surveillance frequency. Studies with integrated surveillance strategies that combine frequent heart rate monitoring with biophysical profile scoring and Doppler report better outcomes and stillbirth rates of between 0% and 4%, compared with those between 8% and 11% with empirically determined surveillance frequency. The variations in clinical behavior and management challenges across gestational age are better addressed when biophysical profile scoring is integrated into the surveillance of fetal growth restriction. This review aims to provide guidance on biophysical profile scoring in the in- and outpatient management of fetal growth restriction.

Key words: biophysical profile, Doppler ultrasound, fetal acidemia, fetal death, fetal growth restriction, fetal hypoxemia, fetal surveillance, nonstress test

Introduction

The management of a fetus with an ultrasound-based weight estimate below the 10th percentile (small for gestational age [SGA]) is a commonly encountered clinical challenge. SGA encompasses fetuses that are constitutionally small but have achieved their growth potential and those where abnormal placental perfusion and gas, nutrient, and fluid exchange leads to fetal growth restriction (FGR).[1–4] This degree of placental dysfunction is the most common precursor to fetal hypoxemia, progressive fetal deterioration, and perinatal morbidity and mortality, requiring a dedicated management approach.[5–9] The consistent application of available surveillance tools in FGR is the foundation for balancing the fetal risks of ongoing monitoring against the neonatal risks associated with delivery, collectively minimizing the risks for stillbirth and iatrogenic delivery.[1–4,8–10]

The guidelines for FGR management differ significantly between national and international organizations.[1,3,8,10–13] Among the available surveillance modalities, only fetal heart rate monitoring by the nonstress test (NST) and umbilical artery (UA) Doppler are universally recommended by all organizations.[12,14] In the United States, the role of the fetal biophysical profile (BPP) as an adjunct to identify fetal hypoxemia or acidemia and to time intervention is only discussed by the American College of Obstetricians & Gynecologists (ACOG)[15]; in contrast, their interpretation of the existing literature led the authors of the recent Society for Maternal-Fetal Medicine (SMFM) guidelines to question the value of the BPP in the management of FGR.[1] Because neither the NST nor the UA Doppler provide the ability to address the spectrum of management challenges

From the Department of Gynecology & Obstetrics, Johns Hopkins Center for Fetal Therapy, Johns Hopkins School of Medicine, Baltimore, MD (Dr Baschat); Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, Colorado Fetal Care Center, Children's Hospital of Colorado, University of Colorado School of Medicine, Aurora, CO (Dr Galan); Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, Baylor College of Medicine, Houston, TX (Dr Lee); Department of Obstetrics & Gynecology, Fetal Diagnostic Center, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA (Dr DeVore); Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, Women's Health Institute, Cleveland Clinic Foundation, Cleveland, OH (Dr Mari); Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, University of Colorado School of Medicine, Aurora, CO (Dr Hobbins); Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, NYU Long Island School of Medicine, New York, NY (Dr Vintzileos); Center for Fetal Medicine and Women's Ultrasound and Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA (Dr Platt); and Fetal Maternal Medicine Consultant, Envision Health, Nashville, TN (Dr Manning).

Received Oct. 16, 2021; revised Jan. 17, 2022; accepted Jan. 21, 2022.

A.A.B. and H.L.G. share first authorship.

L.D.P. and F.A.M. share senior authorship.

The authors report no conflict of interest.

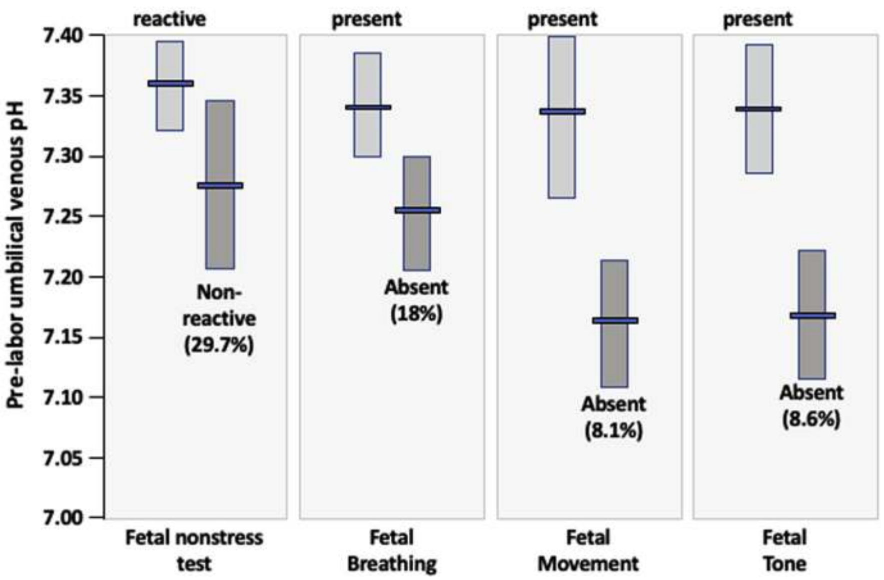
Corresponding author: Ahmet A. Baschat, MD. abascha1@jhmi.edu

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2022.01.020

Click Video under article title in Contents at **ajog.org**

FIGURE 1
Loss of fetal behavioral variables and umbilical venous pH



The bar graph displays the median and interquartile ranges for the umbilical venous pH obtained before delivery in relation to the observations of fetal behaviors.[23,27] The percentages indicate the frequency of the abnormal test findings for each variable. The distribution of pH values is highest for fetuses with a nonreactive nonstress test, lower for those without fetal breathing movements, and lowest when gross body movements or tone are absent. This illustrates the differential sensitivity of the respective regulatory centers to fetal hypoxemia and acidemia termed the "gradual hypoxia concept."

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

encountered in FGR, their use as the central surveillance tools can pose challenges.[3,12,14] This review aims to present the advantages and potential limitations of a BPP and provide guidance on its use in FGR management.

Evolution of Biophysical Profile in Fetal Surveillance

The goals of antepartum surveillance encompass identifying a fetus at risk for in-utero death or injury and to guide interventions that avoid adverse fetal outcome while minimizing neonatal prematurity and subsequent morbidity.[16] This concept relies on the assumption that deteriorating placental function is responsible for the progression of fetal hypoxemia to metabolic acidemia and stillbirth and that these fetal risks can be detected with sufficient certainty to be measured against the neonatal risks of delivery.

The underlying physiology of a biophysical profile

A first fundamental principle of a BPP is that acute fetal activities are not random events but are initiated and regulated in a predictable manner by discrete central nervous system (CNS) centers located in the lower midbrain, pons, and medulla. From the early second trimester onward, these centers generate the neural signals that manifest as a biophysical activity (eg, movement of a fetal limb). Therefore, observation of a biophysical activity can provide insight into the functional integrity of its originating CNS center. The output of these regulatory centers is sensitive to normal modulation by intrinsic sleep-wake cycles typically lasting 20 to 40 minutes[17] and by persistent suppression from hypoxemia and acidemia. Animal experiments and clinical observations in the human fetus have demonstrated that hypoxemia or acidemia can abolish fetal breathing and gross body movements.[18–22] The effect of acid-base status on the NST and fetal tone has not been measured directly but is assumed on the basis of clinical observations.[23]

The threshold level of hypoxemia or acidemia necessary to alter their output varies by the CNS center. The centers that regulate the coupling of fetal movement with heart rate accelerations (reactivity) and fetal breathing movements are most sensitive followed by those regulating fetal movements and finally those controlling fetal tone.[24–28] This physiological phenomenon, called the gradual hypoxia concept, allows for the construction of a cascade of variables, where their loss following the above order during deterioration increases the probability of existing fetal acidemia.[29,30] (Figure 1) The second fundamental principle of a BPP is that fetal hypoxemia or acidemia can trigger aortic arch and carotid body chemoreceptor reflex cardiovascular redistribution, ultimately leading to diminished renal perfusion and oligohydramnios.[29,31]

The technique to perform a biophysical profile

To enhance distinction between physiological (eg, sleep-wake cycles) and abnormal variation in behavior, formal quantification of fetal activity is carried out over 30 minutes, with optional extension to 60 minutes. The modified BPP evaluates the fetal heart rate reactivity and amniotic fluid by ultrasound measurement of the 4-quadrant amniotic fluid index (AFI) or maximum vertical amniotic fluid pocket (MVP) (Table 1).[31] The modified BPP is normal when the NST and amniotic fluid are normal. A nonreactive NST or an abnormal AFI or MVP require further evaluation, typically by a full BPP.[8,32] A full BPP assesses fetal breathing, discrete body movement, fetal tone, and amniotic fluid volume using ultrasound, with optional addition of the NST if these variables are normal (Table 2).[33] Similar to the NST, fetal acoustic stimulation delivered for 1 to 2 seconds by applying an artificial larynx to the maternal abdomen during the BPP can shorten

TABLE 1
Components and criteria for modified biophysical profile

Components	Normal	Abnormal	Follow-up if abnormal
Fetal heart rate testing	Two or more fetal heart rate accelerations during 20 min of observation Magnitude of accelerations should be 10 beats per min over 10 s before 32 weeks' gestation and 15 beats per min over 15 s thereafter[16]	One or no acceleration is detected after 40 min	Full 5-component BPP
Amniotic fluid volume	MVP is greater than 2 cm, the AFI is above 8 cm before 37 weeks or 5 cm thereafter or if the AFI is within the gestational age defined cutoff[117]	Amniotic fluid does not meet criteria	Full 5-component BPP

AFI, amniotic fluid index; *BPP*, biophysical profile; *MVP*, maximum vertical pocket.

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

the testing time and reduce the number of false positives.[34] Two points are assigned for each component meeting the specified criteria, and the final score is classified as normal, equivocal, abnormal, or very abnormal (Table 3).

The classic and modified BPP assume that if a given acute biophysical variable is normal, its CNS regulatory center is not exposed to acidemia; normal amniotic fluid indicates that cardiovascular redistribution has not occurred.[35] Conversely, if an acute variable is persistently absent, acidemia is *a possible cause* and absence of more acute variables indicates that acidemia *is the probable cause*, especially if oligohydramnios is also observed. The relationship between surveillance findings and current fetal acid-base balance is most reliably studied by evaluating cord blood samples obtained prenatally in close temporal relationship or in the absence of labor at cesarean delivery. Using this approach, the relationship between individual fetal activities and acidemia from any underlying cause at the time of testing is well-defined, demonstrating an over 90% correlation of the pH with the overall biophysical score[23,25,27,29,36] (Figure 2, Video 2).

Management on the basis of the biophysical profile in unselected populations

The clinical application of the NST and biophysical variables is guided by underlying physiological principles and their relationships with perinatal outcomes in large nonselected patient populations.[37] The NST as a standalone test has a lower predictive accuracy for hypoxemia or acidemia if nonreactive and a stillbirth rate of 1.9 per 1000 in the following week if reactive.[16] The modified BPP improves accuracy in predicting immediate fetal well-being if normal, but an abnormal test requires assessment of additional behaviors to accurately predict fetal status.[38,39] A normal modified or full BPP is associated with a stillbirth rate of 0.8/1000 in the following week, which is attributable to acute events not reflected in the fetal heart rate or biophysical variables.[40,41] The difference between these levels of reassurance becomes increasingly significant for populations with higher a priori stillbirth risk. These limitations of isolated fetal heart rate testing, even if amniotic fluid is normal, are the rationale for performing a full BPP when the NST is nonreactive or the modified BPP is abnormal. In this setting, the BPP provides a more accurate prediction of the current fetal status and the lowest false negative rate for stillbirth in the following week, and it is the sequence of testing recommended by the ACOG.[8,16]

In unselected populations, the gestational age at initiation and surveillance frequency are typically empirically selected on the basis of the likelihood and anticipated weekly risks for stillbirth. In the absence of other specific

TABLE 2
Components and normal criteria for full biophysical profile

Components	Normal (2 points each)
Fetal heart rate testing	Two or more fetal heart rate accelerations during 20 min of observation Magnitude of accelerations should be 10 beats per min over 10 s before 32 weeks' gestation and 15 beats per min over 15 s thereafter[16]
Fetal breathing	At least 30 s of sustained breathing movements (including hiccups)[123]
Body movement	Three discrete body or limb movements
Fetal tone	One or more episodes of active extensions with return to flexion
Amniotic fluid volume	Maximum fluid pocket >2 cm

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

TABLE 3
Interpretation of biophysical profile score and associated management steps

Interpretation	Findings	Perinatal mortality[a] within 1 week without intervention[41]	Management
Normal	Total score of 10; all components meet criteria Total score of 8; with an amniotic fluid MVP >2 cm	1/1000	Continue current
Equivocal[b]	Total score of 8 but amniotic fluid MVP below 2 cm Total score of 6 with an amniotic fluid MVP >2 cm	89/1000 Variable	Repeat BPP within 24 h with the interval further guided by clinical factors (Table 4)
Abnormal	Total score of 6 with an amniotic fluid MVP below 2 cm Total score of 4	89/1000 91/1000	Evaluate for delivery if persistent
Very abnormal	Total score of 2 Total score of 0	125/1000 600/1000	Deliver

The table summarizes the interpretation of the biophysical profile score with the accompanying findings.

BPP, biophysical profile; *MVP*, maximum vertical pocket; *NST*, nonstress test.

[a] Sum of stillbirths and neonatal deaths within 7 days of birth in pregnancies undergoing fetal surveillance; [b] An equivocal score only excludes acidemia when fetal breathing is present. When the NST is nonreactive and fetal breathing remains absent beyond 60 minutes, the fetal pH may be abnormal requiring additional testing (prolonged NST, inpatient monitoring, repeat testing) to evaluate fetal status.

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

fetal or maternal findings, a normal modified or full BPP does not require modification of the current surveillance strategy. Compared with a normal score, an equivocal result provides less certainty for a normal fetal pH, especially in the absence of fetal breathing. It is also associated with a higher perinatal mortality within a week, requiring an increase in surveillance frequency (Table 3, Figure 2).[13,15,16,36] In the absence of any additional clinical modifiers, an equivocal BPP should be repeated within 24 hours, and further management on the basis of the repeat score at that time should be done. Patients with a persistently equivocal BPP or a score of 4 or less require evaluation for delivery unless the NST is reactive or normal fetal breathing movements are present. The BPP score does not predict the interval when further fetal compromise and further adjustment of surveillance frequency for specific conditions require consideration of the disease characteristics.[3,9,14,39,40]

Validity of the Biophysical Profile in Fetal Growth Restriction With Signs of Abnormal Placentation

The application of any fetal surveillance modality requires the consideration of disease-specific limitations to their reliability.[14,24,42] Abnormal placental function and FGR is associated with delayed development of fetal behavior, cardiovascular deterioration, and variation in overall clinical behavior, all of which could potentially impact the reliability of a biophysical assessment.

Maturation of fetal behavior in the presence of placental dysfunction

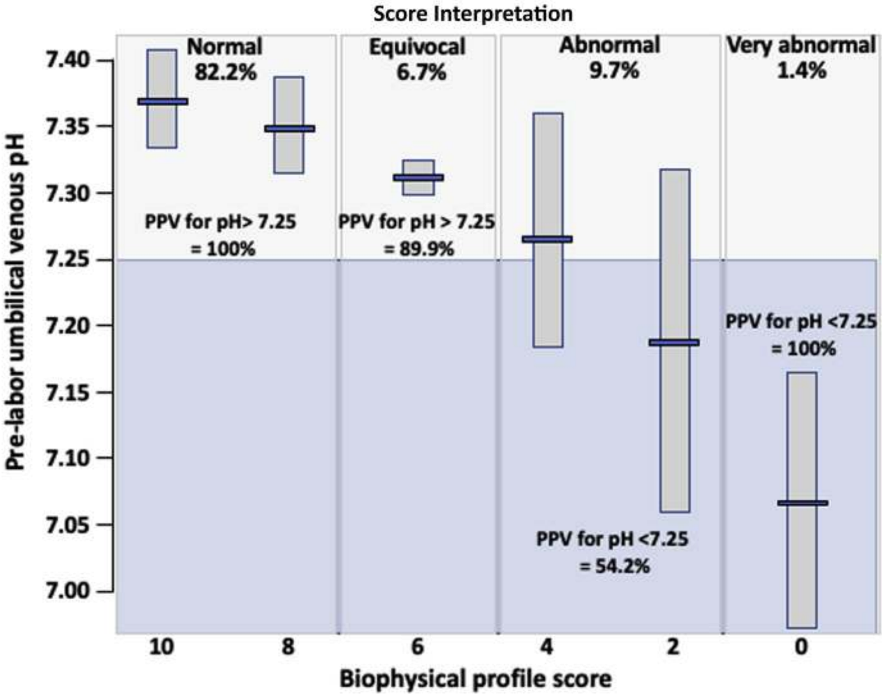
Growth-restricted fetuses have significantly delayed the maturation of behavioral milestones, most notably between 28 to 32 weeks' gestation.[43–47] These delays are responsible for a higher baseline heart rate, lower short- and long-term variability, and a higher prevalence of a nonreactive NST observed in FGR.[48–50] Despite changes in maturation, growth-restricted fetuses retain predictable behavioral responses consistent with the gradual hypoxia concept from 20 weeks onward.[23,27,51–55] Accordingly, prediction of a normal fetal acid-base status by a normal score and acidemia by an abnormal score remains accurate in FGR throughout the second and third trimesters, supporting the use of a BPP at these gestational epochs.

Clinical variation of placental dysfunction and cardiovascular findings

Placental disease in FGR is associated with characteristic cardiovascular abnormalities that are not reflected in a BPP. Placental gas exchange requires adequate maternal and fetal perfusion and efficient diffusion across the maternal-fetal vascular interface.[5] Several placental vascular abnormalities including maternal decidual arteriopathy, massive perivillous fibrinoid, and syncytial knots and fetal distal villous immaturity and thrombotic vasculopathy with a reduction of villous vascular area are observed in FGR and are now labeled as maternal or fetal vascular malperfusion.[56,57] These histologic findings are associated with abnormal villous perfusion or gas diffusion, predisposing growth-restricted fetuses to hypoxemia or acidemia.

Embolization experiments in sheep, pathologic correlation in human pregnancies, and mathematical modeling studies provide insight on the relationship between UA Doppler and the villous vasculature.[58–62] When villous malperfusion affects one-third of the placenta, the umbilical artery blood flow resistance increases measurably, and the end-diastolic velocity becomes absent or reversed (UA A/REDV) when 60% to 70% of the villous resistance vessels are occluded.[57,59] In this setting of high placental blood flow resistance, increased right heart stiffness and myocardial oxygen demand can lead to abnormal ductus venosus (DV) blood flow all the way to reversal during atrial systole.[63−66] It is critical to note that UA and DV Doppler abnormalities are not directly regulated by fetal oxygenation.[67−69] As shown by delivery blood gases, they are associated with the acid-base abnormality that accompanies the degree of placental dysfunction when these Doppler changes occur.[5,14,70−72] In contrast, cerebral autoregulatory vasodilatation (brain sparing) can be directly triggered by decreasing transplacental oxygen diffusion.[73,74] Therefore, brain sparing observed in a small fetus with a normal UA Doppler points toward placental dysfunction predominantly affecting oxygen diffusion rather than villous perfusion. FGR that develops in the second trimester is commonly associated with abnormal villous perfusion, whereas abnormal diffusion is more predominant in third trimester placental pathology, resulting in different characteristic Doppler findings and variation in the clinical picture.[5,9,14,55,56,58,75] More specifically, in early-onset FGR before 32 weeks, UA and DV Doppler define the severity of villous malperfusion-related placental disease. On the contrary, cerebral artery Doppler or perhaps amniotic fluid assessment thereafter, even in patients with normal UA Doppler, points to the presence of diffusion-related placental dysfunction and associated fetal risks that are independent of the growth percentile.[76−82]

FIGURE 2
Biophysical profile score and umbilical venous pH



The bar graph displays the mean and interquartile ranges for the umbilical venous pH obtained by cordocentesis before the onset of labor for BPP test results.[23] The percentages indicate the frequency of individual test score results. The *blue* shaded area indicates an abnormal venous pH below 7.25. The pH values are in the normal range for normal or equivocal scores and abnormal for scores below 6. PPV indicates the positive predictive values for a normal or abnormal pH, respectively.

BPP, biophysical profile.

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

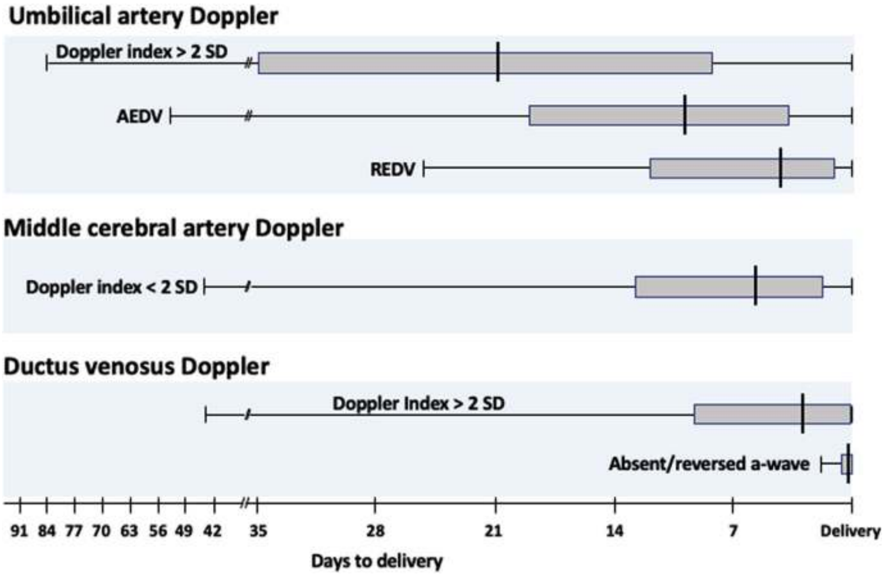
Relationship between cardiovascular and biophysical findings

Because FGR is associated with Doppler findings that reflect the severity of placental dysfunction and the rate of progressive fetal compromise, understanding their relationship with a BPP is important.[48,73,74,83] In principle, fetal cardiovascular abnormalities change over a longer time scale and precede overtly abnormal fetal heart rates tracings or an abnormal BPP (Figure 3).[71,84−86] However, an abnormal fetal heart rate or BPP can develop independent of Doppler findings, and in this setting, reflects the degree of hypoxia or acidemia independent of cardiovascular status.[5,48] In early-onset FGR with an elevated UA Doppler resistance, the daily rate of an abnormal computerized cardiotocography (cCTG) was 5%, and fetal heart rate decelerations requiring delivery increased from 23% to over 30% with an abnormal DV Doppler.[2,84] An equivocal BPP is found in 20% to 30% of early-onset FGR with an abnormal UA Doppler and in 13% to 22% of late FGR with middle cerebral artery (MCA) brain sparing. With appropriate surveillance frequency, there is no evidence that delaying delivery until an abnormal BPP occurs negatively impacts outcome.[86] Accordingly, Doppler abnormalities allow anticipation of fetal deterioration for patients with a normal or equivocal BPP, whereas a decelerative NST or an abnormal BPP provides a safety net for the detection of fetal hypoxemia or acidemia that may not be suspected on the basis of the cardiovascular status alone. Therefore, NSTs and BPP need to be more frequently performed than Doppler ultrasound at a frequency that is guided by the cardiovascular status (Video 2).[14,87,88]

Clinical circumstances and biophysical findings

General criticism about the clinical application of a BPP includes the absence of randomized controlled trials (RCTs) showing benefit,[89,90] the time it

FIGURE 3
Doppler findings and the associated interval to delivery



The bar graph displays the median, range, and interquartile ranges for the timing of delivery in relation to the onset of individual Doppler abnormalities.[74,84,109] A progressive increase in the umbilical artery blood flow resistance or a decrease in the middle cerebral artery blood flow resistance indicates accelerating deterioration of placental function and is associated with shortening of the interval to indicated delivery. In the DV, progression from an elevated Doppler index to loss of forward flow during atrial systole signifies advanced cardiovascular deterioration, and delivery for a variety of fetal indication is expected within a short interval.

AEDV, absent end-diastolic velocity; *DV*, ductus venosus; *REDV*, reversed end-diastolic velocity; *SD*, standard deviation.

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

takes to complete testing, and confounding modification of fetal behavior by medications such as magnesium sulfate[91,92] and corticosteroids.[93] Similar to the NST, there has been no RCT of BPP in FGR management, but its use in other scenarios has been studied.[94,95] The average time to complete a normal BPP is below 5 minutes, and only ruling out an abnormal or equivocal test requires 30 to 60 minutes of direct observation, placing the average time for all tests at just over 18 minutes.[96] The effects of corticosteroids and magnesium are typically transitory and impact fetal behavior and Doppler findings at different intervals from administration, allowing for ongoing fetal assessment when all surveillance modalities are considered.[5,83,97,98]

Specific concerns of the SMFM[1,10] about a BPP in FGR surveillance are based on the Cochrane systematic review[92] and an observational study by Kaur et al.[90] The former has little relevance for FGR management as it mainly included pregnancies with other conditions and did not assess acidemia and stillbirth rates in relation to surveillance strategy.[92] The study by Kaur demonstrated that a BPP does not reliably predict future fetal well-being, as an abnormal NST, stillbirth, or birth acidemia can occur within 4 hours of a normal score.[90] The risk for future deterioration was better stratified by a UA Doppler, and therefore, the authors recommended to supplement the daily BPP with 3 or 4 times daily NSTs in patients with markedly abnormal blood flow.[90] Additional clinical details such as venous Doppler or resuscitative measures are not reported, and the perinatal mortality of 39% identifies this cohort as a unique subset of severe early-onset FGR. The study is in contrast with others, showing that the prediction of fetal acid-base status by BPP is more accurate than a continuous cCTG or DV Doppler even when these modalities are concurrently performed (Figure 4).[14,99] Furthermore, the stillbirth rate of 11% is higher than that of 1% to 4% observed in other early-onset FGR cohorts and is comparable to the 8% observed in late-onset FGR where the surveillance frequency is not adjusted on the basis of Doppler findings.[14,48,74,84,89,90] Conversely, adjusting the frequency of heart rate testing or a BPP on the basis of cardiovascular findings with prospectively defined intervention criteria has yielded the lowest stillbirth and birth acidemia rates for FGR pregnancies with a markedly abnormal UA Doppler.[100]

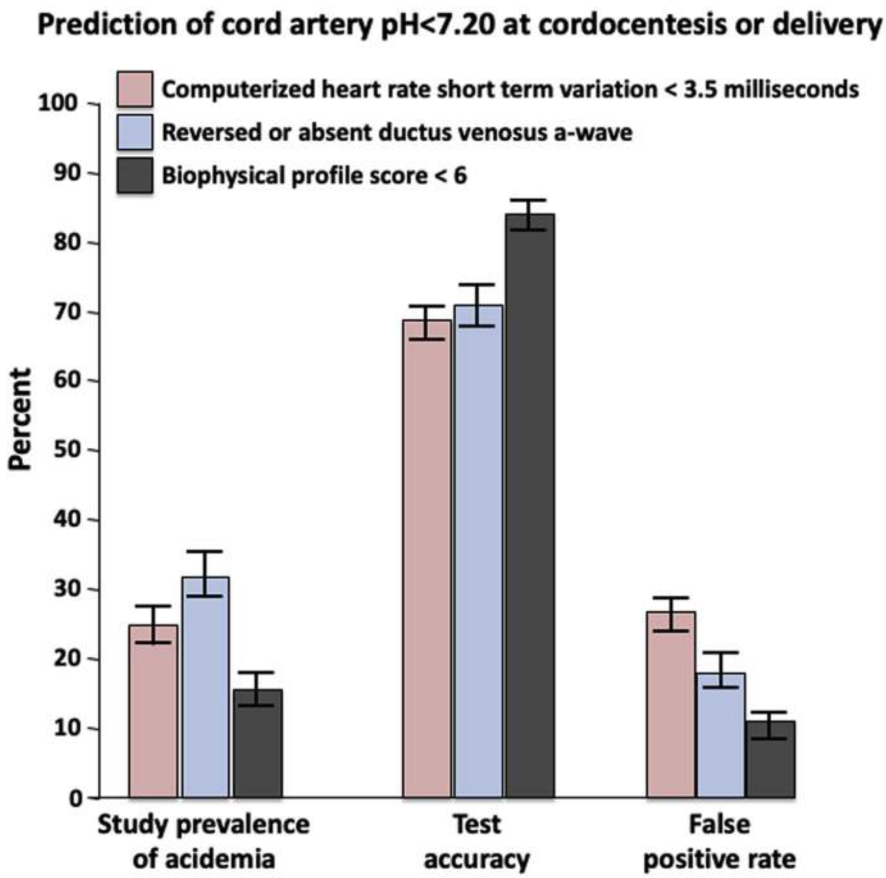
With these associations in mind and their profound impact on the incidence of adverse neonatal and developmental outcomes, the literature does not support to omit a BPP in the management of high-risk pregnancies with FGR.[3,13,14,84,101,102] The primary limitation of a BPP in FGR surveillance is the inability to reliably select optimal surveillance intervals on the basis of the score. Therefore, similar to fetal heart rate testing, its clinical application requires the consideration of Doppler parameters that characterize the severity of placental disease and overall clinical context to inform about the required surveillance frequency in patients with a normal or equivocal BPP score.

Biophysical Profile Considerations Specific to the Management of Fetal Growth Restriction

In the absence of maternal complications, FGR management is guided by the following 3 primary factors: (1) gestational age at presentation, (2) immediate fetal well-being at the time of evaluation, and (3) the anticipated rate of disease progression and fetal deterioration.[2,3,14] The first factor—the gestational age at presentation—determines the inflection point when the benefits of delivery outweigh ongoing surveillance and intervention for fetal status may be considered. Fetal surveillance should be initiated when the decision to intervene for fetal status has been made, and a BPP can be utilized for this purpose as early as at 24 weeks' gestation. However, it is only by 26 weeks' gestation when 50% of delivered growth-restricted neonates, especially those with an estimated fetal weight above 500 g, survive.[103,104] The neonatal mortality, morbidity, and neurodevelopmental delay progressively decline between 26 and 30 weeks, with a residual need for neonatal intensive care admission until 38 weeks' gestation.[7,85,105] From 36 weeks onward, stillbirths for undelivered patients double weekly.[86,106] The delivery threshold is reached when the magnitude and certainty of fetal risks based on surveillance findings exceeds those for the neonate after delivery. Accordingly, advancing gestation shifts the management emphasis from prematurity-tailored delivery thresholds to selecting surveillance intervals for undelivered patients that provide a safety net against unanticipated stillbirth.[3,14] To achieve these goals, surveillance visits have to provide a precise assessment of current fetal status and also the risks for future compromise (Video 2).[74,84]

The other 2 factors (immediate fetal status and disease progression) are driven by the clinical characteristics of FGR, making it necessary to incorporate all aforementioned surveillance modalities into management to offset their individual disadvantages. The specific rationale for including a BPP in FGR management is based on its superior reflection of current fetal acid-base balance, which is independent of fetal heart rate testing and multivessel Doppler.[28,74,91,99] A nonreactive NST is seen in 72% and 30% of early- and late-onset FGR, respectively, and only a normal BPP is validated to establish fetal well-being in this setting.[16] It is critical to note that behavioral responses to deteriorating metabolic status occur independently of Doppler findings and gestational age,[107–113] providing the opportunity for an abnormal BPP to detect fetal compromise not reflected by cardiovascular findings.[29,38,114,115] Conversely, it is equally critical to consider that the Doppler findings provide information about the required surveillance interval, which is independent of the fetal growth percentile even when an NST is reactive or the BPP is normal or equivocal. With the limited use and availability of the cCTG in the US and elsewhere and based on the body of evidence presented above, we propose a surveillance strategy that integrates Doppler and biophysical findings for both ambulatory care and hospitalized pregnancies with FGR. The presented approach is intended to account for the clinical variability in FGR across gestational age.

FIGURE 4
Surveillance modalities and prediction of fetal acidemia at birth



The bar graph displays the test performances of a computerized cardiotocography short-term variation below 3.5 milliseconds, absent or reversed ductus venosus a-wave, and an abnormal biophysical profile score in predicting a cord artery pH <7.20 on cordocentesis or at birth. (Reproduced with permission[14]).

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

Surveillance findings of special relevance

Surveillance findings that are considered absolute delivery criteria at any gestational age include an abnormal BPP, recurrent fetal heart rate decelerations, and a cCTG short-term variation below 2.6 ms or an absent or reversed ductus venosus a-wave if assessed.[2,3,14] An abnormal BPP triggers delivery in 8% to 27%, an abnormal fetal heart rate in 10% to 32%, and an abnormal DV Doppler in 1% to 22% of all FGR pregnancies. From 30 weeks onward, less severe surveillance abnormalities qualify as delivery criteria.[2,3,116] In undelivered patients undergoing serial surveillance, the 3 signs that herald worsening placental dysfunction requiring increasing surveillance frequency irrespective of a reassuring NST or a normal or equivocal BPP are the following: (1)

TABLE 4
Summary of recommendations

1. Fetal surveillance should be initiated when intervention for an abnormal fetal status is considered.
2. The biophysical profile can be used for fetal surveillance in the second and third trimesters.
3. Biophysical profile scoring in fetuses with growth restriction uses the same criteria as in other high-risk pregnancies as follows: Variables can be scored as "present" once they have been observed but require observation of 30 min to be considered "absent." The final biophysical profile score can be assigned once all the variables have been observed or after 30 min and interpreted as follows: normal (8/8; 8/10; 10/10, all with normal amniotic fluid) equivocal (6/10 with normal fluid; 8/10 with abnormal fluid) abnormal (6/10 with abnormal fluid; 4/10) very abnormal (0/10; 2/10)
4. The biophysical profile score assesses current fetal status as follows: A normal score indicates a normal fetal pH at the time of testing irrespective of the Doppler findings. An equivocal score only excludes acidemia when fetal breathing is present. When the NST is nonreactive and fetal breathing remains absent beyond 60 min, the fetal pH may be abnormal, requiring additional testing (prolonged NST, inpatient monitoring, repeat testing) to evaluate the fetal status. An abnormal score indicates that the fetal pH is likely abnormal, requiring consideration for delivery. A very abnormal score indicates the presence of fetal acidemia.
5. In patients with a normal or equivocal biophysical profile score, the surveillance intervals and decision for inpatient monitoring should be based on the following: Doppler ultrasound of the UA, DV, MCA Ultrasound assessment of amniotic fluid volume at the time of testing and its trend over time Changes in maternal status Increased surveillance frequency is required with increasing or new abnormality in these findings irrespective of the biophysical profile score.
6. In the overall surveillance strategy integrating all modalities, the following should be considered: The nonstress test is most frequently performed (twice weekly in the outpatient and up to 4 times daily in the inpatient setting) and requires concurrent availability of biophysical profile scoring. Biophysical profile scoring is required as a backup test for a nonreactive NST or as a standalone surveillance modality and should be performed during any ultrasound evaluation of the fetus. Doppler ultrasound (UA, MCA, DV) is required less often than the NST or BPP but determines the overall surveillance frequency required for these modalities.

BPP, biophysical profile; *DV*, ductus venosus *MCA*, middle cerebral artery; *NST*, nonstress test; *UA*, umbilical artery.

Baschat. Biophysical profile and fetal growth restriction management. Am J Obstet Gynecol 2022.

the loss of UA end-diastolic velocity, (2) abnormal cerebral artery Doppler in late-onset FGR, and (3) declining amniotic fluid volume.[117–119]

Surveillance in the outpatient setting

The outpatient setting poses limitations to surveillance frequency, emphasizing the need for attention to findings that require increased testing. In principle, an NST should be performed more frequently than a Doppler. SMFM currently recommends once weekly NST when UA end-diastolic velocities are forward and more frequent NSTs with UA A/REDV. However, once weekly NST in late-onset FGR carries a stillbirth risk as high as 8% when the MCA Doppler or amniotic fluid are abnormal.[74] Accordingly, we suggest NST twice weekly in this setting. Because the NST is often nonreactive and even a reactive test does not provide anticipation of deterioration, it cannot be used as a standalone test and should at minimum be accompanied by an AFI.[3,74] Because many patients will ultimately require a full BPP for a nonreactive NST, we recommend providing a possibility to carry this out for all outpatients. Any time an ultrasound or Doppler is performed, a concurrent evaluation of the fetal tone, movement and breathing, and amniotic fluid volume is both time-efficient and independently informative. In the absence of other fetal or maternal findings, the BPP should be managed according to the score (Table 3). An increase of surveillance frequency is recommended if the NST is nonreactive in a fetus with a previously reactive heart rate or if the amniotic fluid volume decreases, UA Doppler worsens, or there is a new-onset of MCA dilation, which is observed in 20% to 40% of late FGR with a normal UA Doppler.[120,121] Inpatient management should be considered when surveillance frequency becomes impractical, patient access is a challenge, or maternal preeclampsia develops.

Inpatient surveillance

For patients admitted for fetal surveillance and potential intervention, the NST frequency is once daily at minimum and as frequent as 4 times daily on the basis of the severity of Doppler abnormalities or the maternal condition. A BPP is recommended daily to verify the fetal status if the NST is nonreactive and should accompany all Doppler studies for its ability to detect fetal compromise and stillbirth risk that is not suspected by cardiovascular status.[74,84] Inpatients typically have more severe placental dysfunction, are commonly earlier in gestation, and may receive magnesium sulfate or corticosteroids as part of their management. All of these factors need to be considered in the interpretation of BPP for delivery. Although a BPP of 0 or 2 out of 10 is considered a universal delivery criterion, it is recommended to confirm a score of 4 of 10 over 1 hour before 28 weeks or when other confounders are present. If a DV Doppler is available, the results can be incorporated into delivery decision making as recommended by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and the International Federation of Gynecology and Obstetrics (FIGO).[2,3] The integration of NST, BPP, and arterial and venous Doppler has the greatest potential for improving outcomes in FGR and to significantly decrease iatrogenic prematurity compared with patients managed by UA Doppler alone.[7,14] Delaying delivery until late signs of fetal deterioration are observed carries a risk of stillbirth even in the inpatient setting. In this context, it is important to note that surveillance should not be spaced out if the BPP is normal or equivocal, because the risk of stillbirth within 24 hours remains related to the Doppler abnormalities.[74,92,122] A strategy of daily BPP and twice daily NST with predetermined delivery criteria was associated with no stillbirths even in the setting of a very abnormal UA Doppler.[91]

Conclusion

The management of FGR with placental dysfunction benefits from surveillance tools that complement each other in evaluating fetal status and planning the optimal surveillance interval to preempt fetal damage or demise. A normal or abnormal BPP is the most accurate predictor of current fetal status and the most appropriate follow-up test in patients with a nonreactive NST to determine fetal well-being. The primary limitation of NST and BPP is the inability to predict the rate of progression, requiring the consideration of Doppler to plan surveillance frequency. The independence of BPP deterioration from Doppler findings and the continued prediction of acidemia in this setting makes an abnormal BPP an absolute delivery criterion that can provide a safety net against stillbirth. A BPP can be utilized in any ultrasound resource setting, and accordingly, we recommended including instructions on its application in any SGA management guideline. It is our opinion that despite the recent SMFM statement questioning its value, available evidence supports that the BPP under consideration of the clinical context is a clinically useful management tool in pregnancies complicated by FGR (Table 4, Video 2). ■

REFERENCES

1. Society for Maternal-Fetal Medicine, Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: diagnosis and management of fetal growth restriction: (replaces Clinical Guideline Number 3, April 2012). Am J Obstet Gynecol 2020;223:B2–17.

2. Lees CC, Stampalija T, Baschat A, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol 2020;56:298–312.

3. Melamed N, Baschat A, Yinon Y, et al. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet 2021;152(Suppl1):3–57.

4. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med 1999;340:1234–8.

5. Baschat AA. Fetal responses to placental insufficiency: an update. BJOG 2004;111:1031–41.

6. Zeitlin J, El Ayoubi M, Jarreau PH, et al. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. J Pediatr 2010;157:733–9.e1.

7. Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42:400–8.

8. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics and the Society for Maternal-Fetal Medicine. ACOG Practice Bulletin No. 204: fetal growth restriction. Obstet Gynecol 2019;133:e97–109.

9. Unterscheider J, O'Donoghue K, Daly S, et al. Fetal growth restriction and the risk of perinatal mortality-case studies from the multicentre PORTO study. BMC Pregnancy Childbirth 2014;14:63.

10. Abuhamad A, Martins JG, Biggio JR. Diagnosis and management of fetal growth restriction: the SMFM guideline and comparison with the ISUOG guideline. Ultrasound Obstet Gynecol 2021;57:880–3.

11. Lees C, Stampalija T, Hecher K. Diagnosis and management of fetal growth restriction: the ISUOG guideline and comparison with the SMFM guideline. Ultrasound Obstet Gynecol 2021;57:884–7.

12. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol 2018;218:S855–68.

13. Liston R, Sawchuck D, Young D. No. 197a-fetal health surveillance: antepartum consensus guideline. J Obstet Gynaecol Can 2018;40:e251–71.

14. Baschat AA. Considering evidence in the management of fetal growth restriction. Ultrasound Obstet Gynecol 2021;57:25–8.

15. Fetal growth restriction: ACOG Practice Bulletin, Number 227. Obstet Gynecol 2021;137:e16–28.

16. Signore C, Freeman RK, Spong CY. Antenatal testing-a reevaluation: executive summary of a Eunice Kennedy Shriver National Institute of Child Health and Human Development workshop. Obstet Gynecol 2009;113:687–701.

17. Pillai M, James D. Behavioural states in normal mature human fetuses. Arch Dis Child 1990;65:39–43.

18. Boddy K, Dawes GS, Fisher R, Pinter S, Robinson JS. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. J Physiol 1974;243:599–618.

19. Manning FA, Martin CB Jr, Murata Y, Miyaki K, Danzler G. Breathing movements before death in the primate fetus (Macaca mulatta). Am J Obstet Gynecol 1979;135:71–6.

20. Manning FA, Feyerabend C. Cigarette smoking and fetal breathing movements. Br J Obstet Gynaecol 1976;83:262–70.

21. Dawes GS. The central control of fetal breathing and skeletal muscle movements. J Physiol 1984;346:1–18.

22. Manning FA, Platt LD, Sipos L. Fetal movements in human pregnancies in the third trimester. Obstet Gynecol 1979;54:699–702.

23. Manning FA. Assessment of fetal condition and risk: analysis of single and combined biophysical variable monitoring. Semin Perinatol 1985;9:168–83.

24. Vintzileos AM, Campbell WA, Ingardia CJ, Nochimson DJ. The fetal biophysical profile and its predictive value. Obstet Gynecol 1983;62:271–8.

25. Vintzileos AM, Gaffney SE, Salinger LM, Kontopoulos VG, Campbell WA, Nochimson DJ. The relationships among the fetal biophysical

profile, umbilical cord pH, and Apgar scores. Am J Obstet Gynecol 1987;157:627–31.
26. Vintzileos AM, Campbell WA, Nochimson DJ, Weinbaum PJ. The use and misuse of the fetal biophysical profile. Am J Obstet Gynecol 1987;156:527–33.
27. Vintzileos AM, Fleming AD, Scorza WE, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. Am J Obstet Gynecol 1991;165:707–13.
28. Manning FA, Platt LD, Sipos L. Antepartum fetal evaluation: development of a fetal biophysical profile. Am J Obstet Gynecol 1980;136:787–95.
29. Manning FA, Snijders RJ, Harman CR, Nicolaides KH, Menticoglou S, Morrison I. Fetal Biophysical Profile score. VI. Correlation with antepartum umbilical venous fetal pH. Am J Obstet Gynecol 1993;169:755–63.
30. Vintzileos AM, Lettieri L, Tsapanos V, Campbell WA, Rodis JF. Relationship between combined fetal biophysical activities, oligohydramnios, and fetal acid-base status. J Matern Fetal Neonatal Med 1994;3:64–8.
31. Cohn HE, Sacks EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 1974;120:817–24.
32. Nageotte MP, Towers CV, Asrat T, Freeman RK. Perinatal outcome with the modified biophysical profile. Am J Obstet Gynecol 1994;170:1672–6.
33. Manning FA, Lange IR, Morrison I, Harman CR. Fetal biophysical profile score and the nonstress test: a comparative trial. Obstet Gynecol 1984;64:326–31.
34. Pinette MG, Blackstone J, Wax JR, Cartin A. Using fetal acoustic stimulation to shorten the biophysical profile. J Clin Ultrasound 2005;33:223–5.
35. Clark SL, Sabey P, Jolley K. Nonstress testing with acoustic stimulation and amniotic fluid volume assessment: 5973 tests without unexpected fetal death. Am J Obstet Gynecol 1989;160:694–7.
36. Manning FA. Dynamic ultrasound-based fetal assessment: the fetal biophysical profile score. Clin Obstet Gynecol 1995;38:26–44.
37. Sapoval J, Singh V, Carter RE. Ultrasound biophysical profile. 2021. In: StatPearls Treasure Island. FL: StatPearls; 2022.
38. Manning FA, Morrison I, Harman CR, Menticoglou SM. The abnormal fetal biophysical profile score. V. Predictive accuracy according to score composition. Am J Obstet Gynecol 1990;162:918–24.
39. Manning FA, Platt LD, Sipos L, Keegan KA Jr. Fetal breathing movements and the non-stress test in high-risk pregnancies. Am J Obstet Gynecol 1979;135:511–5.
40. Manning FA, Morrison I, Harman CR, Lange IR, Menticoglou S. Fetal assessment based on fetal biophysical profile scoring: experience in 19,221 referred high-risk pregnancies. II. An analysis of false-negative fetal deaths. Am J Obstet Gynecol 1987;157:880–4.
41. Dayal AK, Manning FA, Berck DJ, et al. Fetal death after normal biophysical profile score: an eighteen-year experience. Am J Obstet Gynecol 1999;181:1231–6.
42. Kontopoulos EV, Vintzileos AM. Condition-specific antepartum fetal testing. Am J Obstet Gynecol 2004;191:1546–51.
43. Arduini D, Rizzo G, Romanini C, Mancuso S. Computerized analysis of behavioural states in asymmetrical growth retarded fetuses. J Perinat Med 1988;16:357–63.
44. Arduini D, Rizzo G, Caforio L, Boccolini MR, Romanini C, Mancuso S. Behavioural state transitions in healthy and growth retarded fetuses. Early Hum Dev 1989;19:155–65.
45. Nijhuis IJ, ten Hof J, Nijhuis JG, et al. Temporal organization of fetal behavior from 24-weeks gestation onwards in normal and complicated pregnancies. Dev Psychobiol 1999;34:257–68.
46. Vindla S, James D, Sahota D. Computerised analysis of unstimulated and stimulated behaviour in fetuses with intrauterine growth restriction. Eur J Obstet Gynecol Reprod Biol 1999;83:37–45.
47. Yum MK, Park EY, Kim CR, Hwang JH. Alterations in irregular and fractal heart rate behavior in growth restricted fetuses. Eur J Obstet Gynecol Reprod Biol 2001;94:51–8.
48. Nijhuis IJ, ten Hof J, Mulder EJ, et al. Fetal heart rate in relation to its variation in normal and growth retarded fetuses. Eur J Obstet Gynecol Reprod Biol 2000;89:27–33.
49. Henson G, Dawes GS, Redman CW. Characterization of the reduced heart rate variation in growth-retarded fetuses. Br J Obstet Gynaecol 1984;91:751–5.
50. Baschat AA, Galan HL, Bhide A, et al. Doppler and biophysical assessment in growth restricted fetuses: distribution of test results. Ultrasound Obstet Gynecol 2006;27:41–7.
51. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relationship of fetal biophysical profile and blood gas values at cordocentesis in severely growth-retarded fetuses. Am J Obstet Gynecol 1990;163:569–71.
52. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses. Br J Obstet Gynaecol 1991;98:820–3.
53. Ribbert LS, Nicolaides KH, Visser GH. Prediction of fetal acidaemia in intrauterine growth retardation: comparison of quantified fetal activity with biophysical profile score. Br J Obstet Gynaecol 1993;100:653–6.
54. Smith JH, Anand KJ, Cotes PM, et al. Antenatal fetal heart rate variation in relation to the respiratory and metabolic status of the compromised human fetus. Br J Obstet Gynaecol 1988;95:980–9.
55. Ribbert LS, Visser GH, Mulder EJ, Zonneveld MF, Morssink LP. Changes with time in fetal heart rate variation, movement incidences and haemodynamics in intrauterine growth retarded fetuses: a longitudinal approach to the assessment of fetal well being. Early Hum Dev 1993;31:195–208.
56. Redline RW. Placental pathology: a systematic approach with clinical correlations. Placenta 2008;29(SupplA):S86–91.
57. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. Arch Pathol Lab Med 2016;140:698–713.
58. Morrow RJ, Adamson SL, Bull SB, Ritchie JW. Effect of placental embolization on the umbilical arterial velocity waveform in fetal sheep. Am J Obstet Gynecol 1989;161:1055–60.
59. Kingdom JC, Burrell SJ, Kaufmann P. Pathology and clinical implications of abnormal umbilical artery Doppler waveforms. Ultrasound Obstet Gynecol 1997;9:271–86.
60. Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. Br J Obstet Gynaecol 1985;92:31–8.
61. Thompson RS, Trudinger BJ. Doppler waveform pulsatility index and resistance, pressure and flow in the umbilical placental circulation: an investigation using a mathematical model. Ultrasound Med Biol 1990;16:449–58.
62. Todros T, Guiot C, Piantà PG. Modelling the feto-placental circulation: 2. A continuous approach to explain normal and abnormal flow velocity waveforms in the umbilical arteries. Ultrasound Med Biol 1992;18:545–51.
63. Devore GR, Horenstein J. Ductus venosus index: a method for evaluating right ventricular preload in the second-trimester fetus. Ultrasound Obstet Gynecol 1993;3:338–42.
64. Baschat AA. Relationship between placental blood flow resistance and precordial venous Doppler indices. Ultrasound Obstet Gynecol 2003;22:561–6.
65. Baschat AA, Gembruch U, Reiss I, Gortner L, Diedrich K. Demonstration of fetal coronary blood flow by Doppler ultrasound in relation to arterial and venous flow velocity waveforms and perinatal outcome–the 'heart-sparing effect'. Ultrasound Obstet Gynecol 1997;9:162–72.
66. Bellotti M, Pennati G, De Gasperi C, Bozzo M, Battaglia FC, Ferrazzi E. Simultaneous measurements of umbilical venous, fetal hepatic, and ductus venosus blood flow in growth-restricted human fetuses. Am J Obstet Gynecol 2004;190:1347–58.
67. Mäkikallio K, Acharya G, Erkinaro T, et al. Ductus venosus velocimetry in acute fetal acidemia and impending fetal death in a sheep model of increased placental vascular resistance. Am J Physiol Heart Circ Physiol 2010;298:H1229–34.
68. Morrow RJ, Adamson SL, Bull SB, Ritchie JW. Acute hypoxemia does not affect the umbilical artery flow velocity waveform in fetal sheep. Obstet Gynecol 1990;75:590–3.
69. Rizzo G, Capponi A, Soregaroli M, Arduini D, Romanini C. Umbilical vein pulsations and acid-

base status at cordocentesis in growth-retarded fetuses with absent end-diastolic velocity in umbilical artery. Biol Neonate 1995;68:163–8.
70. Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation: relationship with fetal blood gases. Am J Obstet Gynecol 1995;173:10–5.
71. Rizzo G, Capponi A, Arduini D, Romanini C. The value of fetal arterial, cardiac and venous flows in predicting pH and blood gases measured in umbilical blood at cordocentesis in growth retarded fetuses. Br J Obstet Gynaecol 1995;102:963–9.
72. Baschat AA, Güclü S, Kush ML, Gembruch U, Weiner CP, Harman CR. Venous Doppler in the prediction of acid-base status of growth-restricted fetuses with elevated placental blood flow resistance. Am J Obstet Gynecol 2004;191:277–84.
73. Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. Br J Obstet Gynaecol 1986;93:471–5.
74. Arbeille P, Maulik D, Fignon A, et al. Assessment of the fetal PO_2 changes by cerebral and umbilical Doppler on lamb fetuses during acute hypoxia. Ultrasound Med Biol 1995;21:861–70.
75. Paules C, Youssef L, Rovira C, et al. Distinctive patterns of placental lesions in preeclampsia vs small-for-gestational age and their association with fetoplacental Doppler. Ultrasound Obstet Gynecol 2019;54:609–16.
76. Baschat AA, Weiner CP. Umbilical artery doppler screening for detection of the small fetus in need of antepartum surveillance. Am J Obstet Gynecol 2000;182:154–8.
77. Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol 2013;208:290.e1–6.
78. Hecher K, Bilardo CM, Stigter RH, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol 2001;18:564–70.
79. Crimmins S, Desai A, Block-Abraham D, Berg C, Gembruch U, Baschat AA. A comparison of Doppler and biophysical findings between liveborn and stillborn growth-restricted fetuses. Am J Obstet Gynecol 2014;211:669.e1–10.
80. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016;48:333–9.
81. Oros D, Figueras F, Cruz-Martinez R, Meler E, Munmany M, Gratacos E. Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses. Ultrasound Obstet Gynecol 2011;37:191–5.
82. Hashimoto K, Kasdaglis T, Jain S, Atkins K, Harman CR, Baschat AA. Isolated low-normal amniotic fluid volume in the early third trimester: association with adverse perinatal outcomes. J Perinat Med 2013;41:349–53.
83. Ferrazzi E, Bozzo M, Rigano S, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 2002;19:140–6.
84. Ganzevoort W, Mensing Van Charante N, Thilaganathan B, et al. How to monitor pregnancies complicated by fetal growth restriction and delivery before 32 weeks: post-hoc analysis of TRUFFLE study. Ultrasound Obstet Gynecol 2017;49:769–77.
85. Boers KE, van Wyk L, van der Post JA, et al. Neonatal morbidity after induction vs expectant monitoring in intrauterine growth restriction at term: a subanalysis of the DIGITAT RCT. Am J Obstet Gynecol 2012;206:344.e1–7.
86. Kahn B, Lumey LH, Zybert PA, et al. Prospective risk of fetal death in singleton, twin, and triplet gestations: implications for practice. Obstet Gynecol 2003;102:685–92.
87. Kaur S, Picconi JL, Chadha R, Kruger M, Mari G. Biophysical profile in the treatment of intrauterine growth-restricted fetuses who weigh <1000 g. Am J Obstet Gynecol 2008;199:264.e1–4.
88. Wolf H, Arabin B, Lees CC, et al. Longitudinal study of computerized cardiotocography in early fetal growth restriction. Ultrasound Obstet Gynecol 2017;50:71–8.
89. Lalor JG, Fawole B, Alfirevic Z, Devane D. Biophysical profile for fetal assessment in high risk pregnancies. Cochrane Database Syst Rev 2008;(1):CD000038.
90. Grivell RM, Wong L, Bhatia V. Regimens of fetal surveillance for impaired fetal growth. Cochrane Database Syst Rev 2012;(6): CD007113.
91. Peaceman AM, Meyer BA, Thorp JA, Parisi VM, Creasy RK. The effect of magnesium sulfate tocolysis on the fetal biophysical profile. Am J Obstet Gynecol 1989;161:771–4.
92. Carlan SJ, O'Brien WF. The effect of magnesium sulfate on the biophysical profile of normal term fetuses. Obstet Gynecol 1991;77:681–4.
93. Deren O, Karaer C, Onderoglu L, Yigit N, Durukan T, Bahado-Singh RO. The effect of steroids on the biophysical profile and Doppler indices of umbilical and middle cerebral arteries in healthy preterm fetuses. Eur J Obstet Gynecol Reprod Biol 2001;99:72–6.
94. Alfirevic Z, Walkinshaw SA. A randomised controlled trial of simple compared with complex antenatal fetal monitoring after 42 weeks of gestation. Br J Obstet Gynaecol 1995;102:638–43.
95. Lewis DF, Adair CD, Weeks JW, Barrilleaux PS, Edwards MS, Garite TJ. A randomized clinical trial of daily nonstress testing versus biophysical profile in the management of preterm premature rupture of membranes. Am J Obstet Gynecol 1999;181:1495–9.
96. Manning FA, Baskett TF, Morrison I, Lange I. Fetal biophysical profile scoring: a prospective study in 1,184 high-risk patients. Am J Obstet Gynecol 1981;140:289–94.
97. Baschat AA. Integrated fetal testing in growth restriction: combining multivessel Doppler and biophysical parameters. Ultrasound Obstet Gynecol 2003;21:1–8.
98. Ott WJ, Mora G, Arias F, Sunderji S, Sheldon G. Comparison of the modified biophysical profile to a "new" biophysical profile incorporating the middle cerebral artery to umbilical artery velocity flow systolic/diastolic ratio. Am J Obstet Gynecol 1998;178:1346–53.
99. Dawes GS, Moulden M, Redman CW. Computerized analysis of the antepartum fetal heart rate. Am J Obstet Gynecol 1995;173:1353–4.
100. Divon MY, Girz BA, Lieblich R, Langer O. Clinical management of the fetus with markedly diminished umbilical artery end-diastolic flow. Am J Obstet Gynecol 1989;161:1523–7.
101. Manning FA, Bondaji N, Harman CR, et al. Fetal assessment based on fetal biophysical profile scoring. VIII. The incidence of cerebral palsy in tested and untested perinates. Am J Obstet Gynecol 1998;178:696–706.
102. Odibo AO, Quinones JN, Lawrence-Cleary K, Stamilio DM, Macones GA. What antepartum fetal test should guide the timing of delivery of the preterm growth-restricted fetus? A decision-analysis. Am J Obstet Gynecol 2004;191:1477–82.
103. Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007;109:253–61.
104. Sharp A, Jackson R, Cornforth C, et al. A prediction model for short-term neonatal outcomes in severe early-onset fetal growth restriction. Eur J Obstet Gynecol Reprod Biol 2019;241:109–18.
105. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M; GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet 2004;364:513–20.
106. Trudell AS, Tuuli MG, Cahill AG, Macones GA, Odibo AO. Balancing the risks of stillbirth and neonatal death in the early preterm small-for-gestational-age fetus. Am J Obstet Gynecol 2014;211:295.e1–7.
107. Pillai M, James D. Continuation of normal neurobehavioural development in fetuses with absent umbilical arterial end diastolic velocities. Br J Obstet Gynaecol 1991;98:277–81.
108. Arduini D, Rizzo G, Capponi A, Rinaldo D, Romanini C. Fetal pH value determined by cordocentesis: an independent predictor of the development of antepartum fetal heart rate decelerations in growth retarded fetuses with absent end-diastolic velocity in umbilical artery. J Perinat Med 1996;24:601–7.
109. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 2001;18:571–7.

110. Rizzo G, Arduini D, Pennestri F, Romanini C, Mancuso S. Fetal behaviour in growth retardation: its relationship to fetal blood flow. Prenat Diagn 1987;7:229–38.
111. Cosmi E, Ambrosini G, D'Antona D, Saccardi C, Mari G. Doppler, cardiotocography, and biophysical profile changes in growth-restricted fetuses. Obstet Gynecol 2005;106:1240–5.
112. Turan S, Turan OM, Berg C, et al. Computerized fetal heart rate analysis, Doppler ultrasound and biophysical profile score in the prediction of acid-base status of growth-restricted fetuses. Ultrasound Obstet Gynecol 2007;30:750–6.
113. Lai J, Nowlan NC, Vaidyanathan R, Visser GHA, Lees CC. The use of actograph in the assessment of fetal well-being. J Matern Fetal Neonatal Med 2020;33:2116–21.
114. McCowan LM, Harding JE, Roberts AB, Barker SE, Ford C, Stewart AW. A pilot randomized controlled trial of two regimens of fetal surveillance for small-for-gestational-age fetuses with normal results of umbilical artery doppler velocimetry. Am J Obstet Gynecol 2000;182:81–6.
115. Turan OM, Turan S, Gungor S, et al. Progression of Doppler abnormalities in intrauterine growth restriction. Ultrasound Obstet Gynecol 2008;32:160–7.
116. Lees CC, Marlow N, van Wassenaer-Leemhuis A, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet 2015;385:2162–72.
117. Manning FA, Hill LD, Platt LD. Qualitative amniotic fluid volume determination by ultrasound: antenatal detection of intrauterine growth restriction. Am J Obstet Gynecol 1981;193:254–8.
118. Chamberlain PF, Manning FA, Morrison I, Harman CR, Lange IR. Ultrasound evaluation of amniotic fluid volume. I. The relationship of marginal and decreased amniotic fluid volumes to perinatal outcome. Am J Obstet Gynecol 1984;150:245–9.
119. Hernandez-Andrade E, Stampalija T, Figueras F. Cerebral blood flow studies in the diagnosis and management of intrauterine growth restriction. Curr Opin Obstet Gynecol 2013;25:138–44.
120. Eixarch E, Meler E, Iraola A, et al. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. Ultrasound Obstet Gynecol 2008;32:894–9.
121. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Changes in myocardial performance index and aortic isthmus and ductus venosus Doppler in term, small-for-gestational age fetuses with normal umbilical artery pulsatility index. Ultrasound Obstet Gynecol 2011;38:400–5.
122. Turan OM, Turan S, Berg C, et al. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 2011;38:295–302.
123. Pillai M, James D. Hiccups and breathing in human fetuses. Arch Dis Child 1990;65:1072–5.